# Alerts, Notices, and Case Reports

## Arterial Thrombosis in Ulcerative Colitis
### Transcatheter Thrombolytic Therapy

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THROMBOEMBOLISM has been recognized as a rare but serious complication of inflammatory bowel disease since six cases were first described in 1936.[1] Case studies and reviews since then have emphasized the poor prognosis associated with thrombosis. Two thirds of cases have been due to deep venous thrombi or pulmonary embolic events.[2] Some reports have discussed the diagnosis and treatment of venous thrombosis, but effective management of extensive arterial thrombosis associated with inflammatory bowel disease has not been previously described. We report the occurrence of bilateral lower extremity arterial thrombosis in a patient recently diagnosed with inflammatory bowel disease. Circulation was restored with the transcatheter intrathrombic administration of urokinase (Abbokinase; Abbott Laboratories, North Chicago, Illinois).

### Report of a Case

The patient, a 27-year-old woman, was admitted to the University of California, Davis, Medical Center (Sacramento) because of crampy abdominal pain, watery diarrhea, and tenesmus. She reported that for the past five days leg cramps had developed after she walked short distances, and on the evening before admission, her left leg became numb and she was unable to bear weight on it. She also had some numbness in the fingers of her right hand. Five months before admission, flexible sigmoidoscopy and biopsies of the sigmoid colon showed ulcerative colitis. She was initially treated with sulfasalazine, but was switched to high-dose oral prednisone for improved control. At the time of admission to the medical center, she had been taking 60 mg of prednisone each day. She was also taking birth control pills.

On physical examination, she was afebrile, with a diffusely tender abdomen. Her right index finger was noted to be cyanotic, cool, and numb distally. Her peripheral pulses were intact, without bruits. She had decreased sensation to light touch in both feet, worse on the left.

Laboratory analysis revealed a hemoglobin concentration of 77 grams per liter (7.7 grams per dl), a hematocrit of 0.24 (24%), a leukocyte count of $9.2 \times 10^9$ per liter (9,200 per $mm^3$), and a platelet count of $402 \times 10^9$ per liter (402,000 per $mm^3$). The serum concentrations of sodium, potassium, chloride, bicarbonate, creatinine, urea nitrogen, alkaline phosphatase, alanine aminotransferase, γ-glutamyltransferase, and total bilirubin were within normal limits. The albumin concentration was 26 grams per liter (2.6 grams per dl). The prothrombin time was 11.5 seconds, which is within the normal range. Her stool was guaiac-positive.

For her colitis, the patient was treated with a regimen of 80 mg per day of prednisone and intravenous cyclosporine. A course of nifedipine was started for presumed Raynaud's phenomenon affecting the right index finger. Flexible sigmoidoscopy was done to 40 cm. From 20 to 40 cm, several large, widely spaced ulcers with patchy erythema were seen. The intervening mucosa appeared normal. Gastrointestinal blood loss was treated by transfusion. Autoimmune vasculitis was excluded by negative tests for antinuclear antibodies and rheumatoid factor; the C3, C4, and protein S levels were normal. A protein C level was 68% (74% to 137% of normal human plasma).

Further evaluation was conducted for a hypercoagulable state, specifically the primary antiphospholipid syndrome. This revealed phosphatidylserine immunoglobulin (Ig) antibody IgG, IgM, and IgA levels all elevated greater than 2 standard deviations. Also, the anticardiolipin antibody IgG level was 21 phospholipid units per ml (normal, < 15). Three days after admission, the patient had the sudden development of severe left leg and left foot pain and an inability to flex or extend the left foot or toes. Physical examination revealed her left foot to be pulseless and cold. The patient's steroid and birth control drugs were discontinued because they may have contributed to a hypercoagulable state.

She was referred to the interventional radiology service for consultation. Biplane aortography with bilateral lower extremity runoff was done and showed normal aortic and visceral vascular anatomy. Small thrombi were demonstrated in the right internal iliac artery and in distal branches of the right deep femoral artery (Figure 1-A). There was occlusion of the right infragenicular popliteal artery (Figure 1-B). Thrombus was demonstrated in the right posterior tibial, anterior tibial, and peroneal arteries. No flow was seen past the right midcalf (Figure 1-B). The left side showed total occlusion of the distal common femoral artery with thrombus seen in the deep left femoral artery (Figure 1-A). Eventually segmental reconstitution of the distal superficial femoral

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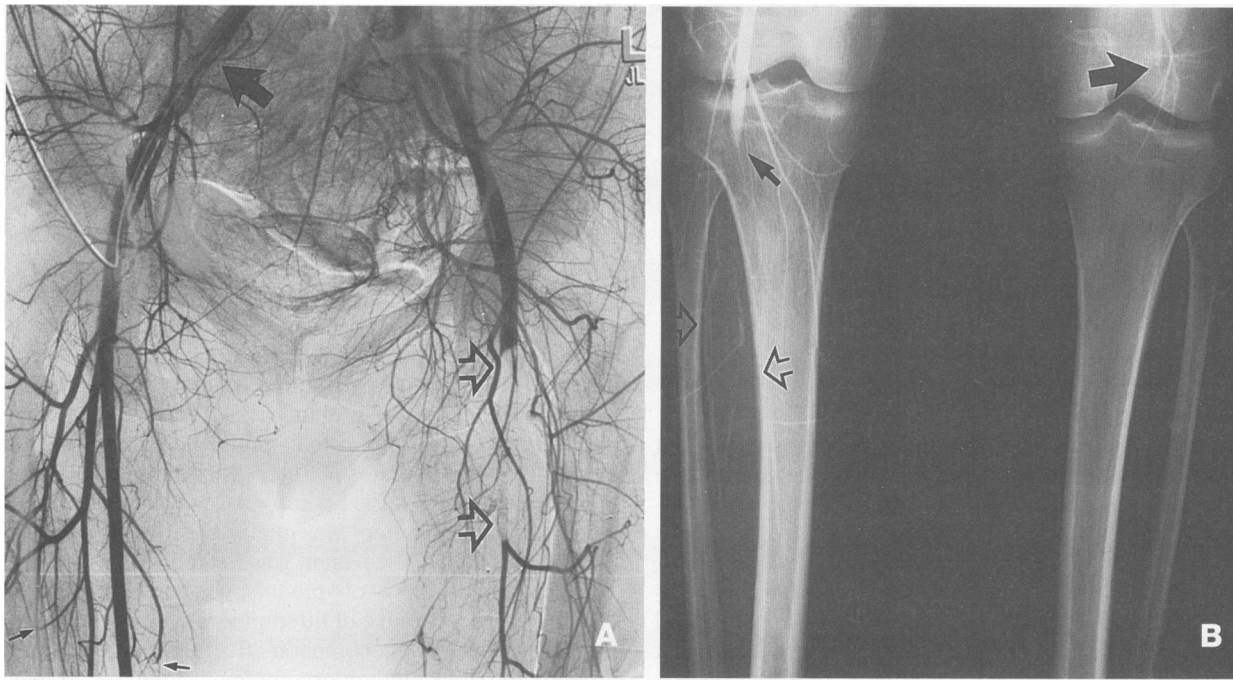


**Figure 1.**—Before treatment, **A**, subtraction angiogram of the pelvis and upper thighs shows thrombus in the right internal iliac artery **(large solid arrow)** and distal branches of the right deep femoral artery **(small solid arrows)**. There is occlusion of the left common femoral artery and thrombus in the left deep femoral artery **(open arrows)**. **B**, Cut-film arteriography shows thrombus in the anterior tibial, common tibioperoneal, peroneal, and posterior tibial arteries **(open arrows)**. There is occlusion of the right infragenicular popliteal artery **(small solid arrow)**. No flow is seen past the left popliteal artery at the level of the knee **(large solid arrow)**.

artery and occlusion of the supragenicular popliteal artery occurred. No flow was demonstrated past the level of the knee joint on the left side (Figure 1-B).

The patient underwent transesophageal echocardiography and duplex Doppler evaluation of the lower extremities. There was no evidence of peripheral deep venous thrombosis, intracardiac anatomic abnormalities, or intracardiac thrombus; therefore, a provisional diagnosis of in situ arterial thromboembolism was made. Consultation was obtained with staff from the Department of Vascular Surgery. Because of the multiple sites of thrombosis and the possibility of a vasoplastic component, a trial of catheter-directed intrathrombic thrombolytic therapy was attempted. Should this fail, surgical thrombectomy would then be attempted.

*Treatment*

Because of a progressive loss of motor function and sensation, we initially concentrated on treating the patient's left leg. Thrombolytic therapy was begun using the pulse-spray pharmacomechanical thrombolytic technique as described elsewhere.[3,4] This was accomplished by passing a guide wire into the thrombus in the common and superficial femoral arteries. This was exchanged for a multiple–side-hole catheter. A mixture of 250,000 IU of urokinase in 9 ml of normal saline solution and 1 ml of 5,000 IU of heparin per milliliter was prepared. Repeated small-volume (0.2 to 0.4 ml), high-pressure injections of concentrated urokinase solution were made into the occluding thrombus. Once flow was established into the occluded vessel, the catheter was secured in place. The infusion technique of urokinase delivery was then initiated.[5,6] A mixture of 250,000 IU of urokinase in 62.5 ml of a solution of 5% dextrose in water was infused at 4,000 IU per minute (about 60 ml per hour). This was maintained for 1 hour, followed by 2,000 IU per minute (30 ml per hour) for 2 hours and then 1,000 IU per minute (15 ml per hour) for 16 hours. Systemic anticoagulation was maintained with the intravenous administration of heparin. We attempted to maintain a partial thromboplastin time between a range of 60 and 80 seconds during her course of thrombolytic therapy. Nifedipine administration was continued to treat any vasospastic component of her thrombotic state. Fibrinogen levels were closely monitored to evaluate for a systemic lytic state. On the second day of thrombolysis directed toward the left lower extremity, the fibrinogen level decreased from 2.3 to 0.8 grams per liter (226 to 78 mg per dl). The urokinase infusion was discontinued, heparin therapy was continued, and fresh frozen plasma was transfused. Her fibrinogen level increased to 1.9 grams per liter (192 mg per dl). The patient underwent follow-up arteriography the next morning. Moderate residual thromboemboli remained, and therapy directed at the left lower extremity was extended for about 72 hours with intermittent arteriography to evaluate for the progression of thrombolysis. After a total of 3.5 million IU of urokinase was administered, the left posterior tibial and dorsalis pedis pulses returned, and the left leg became warm and viable.

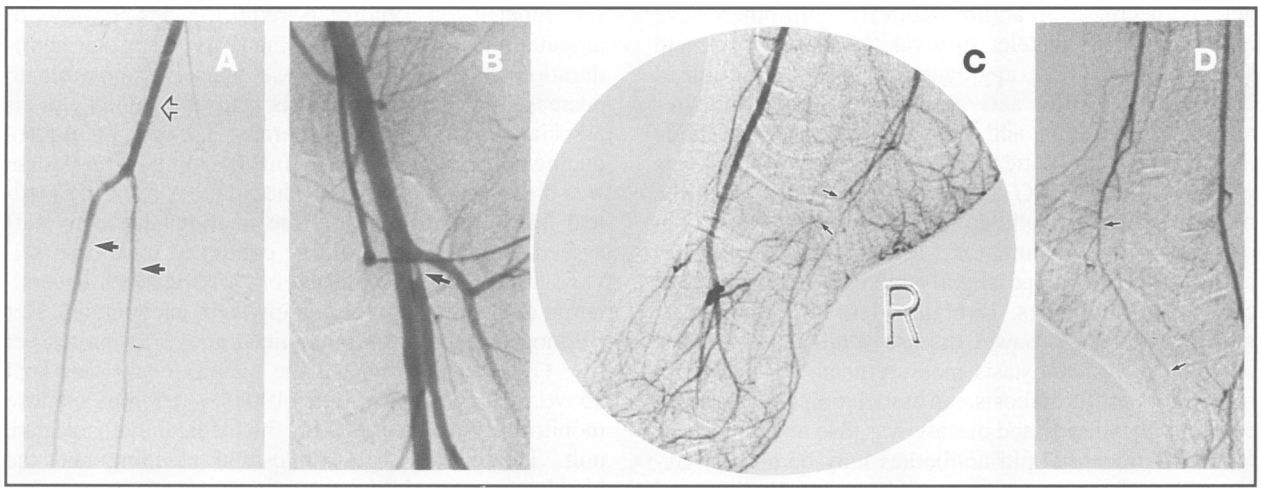


**Figure 2.**—After treatment, **A**, digital subtraction angiogram of the right lower extremity shows patency of the right popliteal **(open arrow)** and posterior and anterior tibial arteries **(closed arrows)**. There is persistent occlusion of the peroneal artery. **B**, Digital subtraction angiogram of the left proximal femoral region shows a small amount of nonoccluding thrombus in the descending branch of the left deep femoral artery **(closed arrow)**. The common femoral, deep femoral, and superficial femoral arteries are otherwise patent. **C**, Digital subtraction angiography of the right foot shows occlusion consistent with small thrombi in the plantar arch of the right foot **(small closed arrows)**. **D**, Digital subtraction angiography of the left foot shows evidence of small thrombi within the plantar arch and distal posterior tibial artery **(small closed arrows)**.

The right leg began showing evidence of worsening ischemia with some loss of sensation on the day that transcatheter therapy was completed on the left. A multiple–side-hole infusion catheter was positioned in the right popliteal artery, and the guide wire was passed down the trifurcation vessels. Using both pulse-spray and infusion techniques, a total of 2.25 million IU of urokinase was administered to the right leg over approximately 36 hours. The patient showed pronounced improvement in the perfusion of the right leg, with the return of near-normal sensation and motor function. Systemic anticoagulation was maintained with heparin throughout the course of thrombolytic therapy. The partial thromboplastin time was maintained in the 60- to 80-second range. Antiplatelet therapy was withheld with the hopes of minimizing gastrointestinal blood loss. Also, the thought was that if hemorrhagic complications recurred, heparin and urokinase therapy could be rapidly reversed, whereas platelet inactivation would require additional transfusions.

Because of the development of hematochezia and bleeding into the right forearm from previous radial arterial punctures for blood gas measurements, thrombolytic therapy was discontinued on hospital day 6. Fortunately, the patient's lower extremity perfusion had improved bilaterally, and she was no longer at risk for limb loss. After the development of bright red bleeding per rectum on hospital day 6, her hematocrit dropped from about 0.40 to 0.33 (40% to 32.6%) and remained stable. No further blood transfusions were required. Because of the patient's previous endoscopy showing several large widely spaced ulcers in her sigmoid colon, this was presumed to be the source of bleeding, and no further colonoscopy was done. After the discontinuation of thrombolytic and anticoagulation therapy, the patient's gastrointestinal bleeding resolved.

Final arteriographic evaluation of the left leg (on hospital day 4) and the right leg (on hospital day 6) showed widely patent vasculature with minimal thrombus seen in the left deep femoral artery (Figure 2-B), distal left posterior tibial arterial branches, and left plantar arch (Figure 2-D). There was persistent occlusion of the right peroneal artery (Figure 2-A) and a small amount of thrombus in branches of the plantar arch of the right foot (Figure 2-C). Anticoagulation therapy was changed from heparin to warfarin sodium, and she was discharged after four weeks of hospital stay with good pulses distally and improved lower extremity strength.

The patient is currently doing well 1½ years after her episode of arterial thromboembolism. She has been on long-term warfarin therapy without recurrent symptoms of lower extremity ischemia.

## Discussion

In 1936 a total of 18 cases of thrombophlebitis or arterial thrombosis occurred among 1,500 cases of chronic ulcerative colitis.[1] A series of 7,199 patients with inflammatory bowel disease were observed from 1970 to 1980 at the Mayo Clinic (Rochester, Minnesota), and thromboembolic complications were found in 92 (1.3%).[7] Of these 92 cases, only 7 involved peripheral arterial thrombosis.

The cause for the association of thromboembolism and inflammatory bowel disease is not clear. Bargen and Barker suggested several mechanisms: stasis from bed rest, severe infection, local damage to the large iliac veins due to neighboring peritonitis, and propagation from small rectal veins.[1] Other investigators have found increases in coagulation factors V and VII and fibrino-

gen and decreases in antithrombin III.[8] Still others have noted decreased platelet survival, thrombocytosis, and spontaneous platelet aggregation.[9] One author linked coagulation with activation of the monocyte-macrophage system and the release of fibrinopeptide A.[10] As noted, this patient had borderline elevated levels of anticardiolipin IgG antibody. In another report, the risk of thromboembolic complications was reviewed in patients with inflammatory bowel disease.[11] Of 20 patients studied, 6 had slightly increased titers of anticardiolipin antibodies. Overall, 14 of the 20 patients with inflammatory bowel disease studied had at least one change in hemostasis measurements considered as risk factors for thrombosis. An association between anticardiolipin antibody and disease was also noted in a case report.[12] Anticardiolipin antibodies may be an underlying cause of the association of thromboembolism and inflammatory bowel disease.

Although arterial thrombosis is a relatively rare complication of ulcerative colitis, its occurrence has been associated with a poor prognosis.[1,7,13,14] The need for early diagnosis is important because effective therapy is now available. Of 60 cases at autopsy, thromboembolism was cited as the cause of death in 7.[14] In another report, thrombi and emboli were present in 14 of 43 patients dying of inflammatory bowel disease,[1] and 23 of 92 patients (25%) died during a thromboembolic complication.[7] Two groups of patients had a substantial risk of mortality: those with recurrent deep venous thrombosis and pulmonary emboli associated with exacerbations of their disease, and those with septicemia that develops as a complication of severe inflammatory bowel disease or a surgical procedure.

The most effective treatment of thrombosis occurring in a patient with inflammatory bowel disease has not been established. Streptokinase was reportedly successful in the treatment of extensive venous thrombosis.[9] Until now, however, in the few cases of arterial thrombosis described in the literature, patients have been treated with surgical embolectomy. Consultation with our vascular surgical colleagues resulted in a decision to first attempt transcatheter thrombolytic therapy, to be followed by surgical embolectomy should transcatheter therapy fail. Because of the several sites and extensive degree of thrombosis, numerous arteriotomies and surgical thromboembolectomies would have been required. We thought that the less invasive transcatheter therapy would have a good chance for success and did not preclude surgical thromboembolectomy should transcatheter therapy fail. Our experience indicates that thrombolytics may also be useful for extensive as well as multiple arterial thromboses.

The overall risk of complications of thrombolytic therapy ranges between 3% and 28%, with the incidence of major complications ranging between 3% and 11.5%.[15,16] The most common complication of thrombolytic therapy is hemorrhage. Other possible complications include distal embolization, pericatheter thrombosis, reperfusion syndrome requiring fasciotomy, or amputation.[15] Attempts were made to administer short-duration pulse-spray urokinase whenever possible to decrease the systemic effects and the complications associated with urokinase therapy. The risk of reintroducing additional gastrointestinal bleeding in our patient was discussed at length with her and her referring medical team. The patient and the treating physician staff agreed that therapy would be continued until limb salvage had been accomplished or complications necessitating discontinuation of therapy were encountered. Her fibrinogen levels were maintained above 1.0 grams per liter (100 mg per dl), and the platelet count was kept above $100 \times 10^9$ per liter (100,000 per $mm^3$). Close monitoring was maintained in the medical intensive care unit. The patient's gastrointestinal bleeding and the bleeding into the right forearm occurred at a point in her treatment when limb salvage had been accomplished. Therefore, we felt that the risk of continued urokinase therapy was outweighed by the risk of bleeding.

For some patients, long-term anticoagulation has been successful in preventing recurrent thrombosis.[17] Warfarin therapy, however, presents additional risks for patients who have a predisposition for gastrointestinal hemorrhage. Partial obstruction of the vena cava with an umbrella or clip has been advocated as a way to prevent pulmonary emboli in patients with venous thrombosis.[7] In some cases, colectomy may be indicated, as this has been shown to prevent the recurrence of the systemic complications of inflammatory bowel disease.[18]

The transcatheter intrathrombic administration of urokinase provides an attractive alternative to surgical embolectomy for the treatment of arterial thromboembolic complications of inflammatory bowel disease.

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# Unilateral Femoral Pistol-Shot Sounds
## A Clue to Aortic Dissection

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THE FEMORAL "PISTOL-SHOT SOUND" is a short, loud, snapping sound heard with the stethoscope over both femoral arteries in some patients with severe aortic regurgitation. These sounds are identical to the Korotkoff sounds elicited in the brachial artery during blood pressure measurements. Although femoral pistol-shot sounds are usually bilateral, we describe the case of a patient with unilateral pistol-shot sounds who was found to have a type B aortic dissection (without aortic regurgitation) involving the artery immediately proximal to where the sound was discovered.

### Report of a Case

The patient, a 69-year-old man with hypertension and an ectatic thoracic aorta, was transferred to the Seattle (Washington) Veterans Affairs Medical Center in March 1989 with severe chest pain. Examination revealed a blood pressure in both arms of 160/92 mm of mercury, a pulse of 76 beats per minute, a midsystolic apical murmur, and symmetric pulses in the neck and upper and lower extremities. There was no diastolic murmur. Auscultation of the right femoral artery was remarkable for a short, loud, snapping sound with each pulse (pistol-shot sound). No pistol-shot sound was heard over the left femoral or brachial arteries.

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A chest x-ray film revealed a massively dilated aortic arch and descending thoracic aorta. Aortography showed a type B aortic dissection beginning at the left subclavian artery and extending at least to the level of the renal arteries, possibly as far as the right common iliac artery. No aortic regurgitation was seen. The patient did well with conservative management that consisted of a regimen of metoprolol tartrate, isosorbide dinitrate, and nifedipine.

Four years later, a magnetic resonance scan confirmed that the dissection had extended at least to the level of the right common iliac artery (Figure 1).

### Discussion

Femoral pistol-shot sounds usually result from the sudden expansion and tensing of the walls of the femoral arteries during systole,[1] and consequently, they are associated with the wide pulse pressures seen in patients with aortic regurgitation and in normal persons after receiving peripheral vasodilators, such as tolazoline hydrochloride.[2] The sounds are analogous to the loud, snapping notes heard when a sail or parachute suddenly fills with wind. The quicker the vessel dilates, the louder the note, and in patients with aortic regurgitation, the intensity of the pistol-shot sound correlates with the height of the pulse pressure[3] and the change in pressure over time (dP/dt) of the pulse.[2]

Abrupt expansion of other large vessels may produce similar sounds, such as the venous pistol-shot sound (sudden dilation of the jugular and femoral veins by the systolic venous wave of severe tricuspid regurgitation),[4] the presystolic snapping jugular sound (abrupt tensing of the jugular vein by a giant A wave in patients with right atrial hypertension),[5] the double femoral sound (found in patients with severe pulmonary hypertension, the first component being venous from right atrial systole and the second being arterial from left ventricular systole),[6] and the Korotkoff sounds. Korotkoff sounds occur because the artery underneath the constricting cuff collapses and suddenly opens with each beat when sphygmomanometer pressures are between the patient's systolic and diastolic blood pressure (the artery opens because the systolic pressure is greater than the cuff pressure; it collapses because the cuff pressure is greater than diastolic pressure).[1,7] When the cuff pressure falls below the patient's diastolic pressure, the artery no longer collapses and the sound disappears.

Previous large studies that reviewed the clinical findings of patients with aortic dissection fail to include a description of the unilateral femoral pistol-shot sound,[8-10] although in one patient with a type A dissection extending to the right internal iliac artery, a "double, metallic, clicking sound," synchronous with each pulse, was heard over the abdominal aorta for a period of 12 hours.[11]

The unilateral pistol-shot sound in our patient appeared immediately downstream from the distal end of his type B dissection (the right common iliac artery). When the sound was first noted, our patient was not